

A Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies

Megan E. Piper, PhD; Stevens S. Smith, PhD; Tanya R. Schlam, PhD; Michael C. Fiore, MD, PhD; Douglas E. Jorenby, PhD; David Fraser, MS; Timothy B. Baker, PhD

Context: Little direct evidence exists on the relative efficacies of different smoking cessation pharmacotherapies, yet such evidence is needed to make informed decisions about their clinical use.

Objective: To assess the relative efficacies of 5 smoking cessation pharmacotherapy interventions using placebo-controlled, head-to-head comparisons.

Design: A randomized, double-blind, placebo-controlled clinical trial.

Setting: Two urban research sites.

Patients: One thousand five hundred four adults who smoked at least 10 cigarettes per day during the past 6 months and reported being motivated to quit smoking. Participants were excluded if they reported using any form of tobacco other than cigarettes; current use of bupropion; having a current psychosis or schizophrenia diagnosis; or having medical contraindications for any of the study medications.

Interventions: Participants were randomized to 1 of 6 treatment conditions: nicotine lozenge, nicotine patch, sustained-release bupropion, nicotine patch plus nico-

tine lozenge, bupropion plus nicotine lozenge, or placebo. In addition, all participants received 6 individual counseling sessions.

Main Outcome Measures: Biochemically confirmed 7-day point-prevalence abstinence assessed at 1 week after the quit date (postquit), end of treatment (8 weeks postquit), and 6 months postquit. Other outcomes were initial cessation, number of days to lapse, number of days to relapse, and latency to relapse after the first lapse.

Results: All pharmacotherapies differed from placebo when examined without protection for multiple comparisons (odds ratios, 1.63-2.34). With such protection, only the nicotine patch plus nicotine lozenge (odds ratio, 2.34, $P < .001$) produced significantly higher abstinence rates at 6-month postquit than did placebo.

Conclusion: While the nicotine lozenge, bupropion, and bupropion plus lozenge produced effects that were comparable with those reported in previous research, the nicotine patch plus lozenge produced the greatest benefit relative to placebo for smoking cessation.

Arch Gen Psychiatry. 2009;66(11):1253-1262

Author Affiliations: Center for Tobacco Research and Intervention (Drs Piper, Smith, Schlam, Fiore, Jorenby, and Baker and Mr Fraser), and Department of Medicine (Drs Smith, Fiore, Jorenby, and Baker), University of Wisconsin School of Medicine and Public Health, Madison.

MANY SMOKERS HAVE successfully quit using a variety of smoking cessation pharmacotherapies, yet there is little direct evidence on the relative efficacies of these different pharmacotherapies. Without such evidence clinicians and smokers lack a strong empirical basis for recommending or selecting among them. We report data on the efficacies of 5 different smoking cessation pharmacotherapies. This research also evaluates the efficacy of the nicotine lozenge, providing additional information on a treatment that has been supported by only 1 placebo-controlled study published to date. Finally, this research evaluates 2 different

medication combinations, one of which (ie, the nicotine patch plus nicotine lozenge) has not been previously evaluated.

There is a great deal of evidence that smoking cessation medications increase the success of attempts to quit smoking.¹⁻⁴ The 2008 Update to the Public Health Service (PHS) Treating Tobacco Use and Dependence Clinical Practice Guideline found that 5 nicotine replacement therapies (NRTs) and 2 non-nicotine replacement first-line pharmacotherapies (sustained-release bupropion [bupropion SR] and varenicline) reliably increase abstinence rates relative to a placebo control.¹ However, less is known about the relative efficacies of these medications. This limitation is due, in part, to a lack of clinical trials that provide head-to-

head comparisons of different pharmacotherapies within the same study. Cessation studies of individual medications differ in myriad respects, which makes it difficult to gauge effectiveness across treatments, even when the individual studies contain a placebo control for the medication. Meta-analyses that attempt to account for interstudy differences may yield conclusions that conflict markedly with large-scale head-to-head trials.⁵ Without evidence based on head-to-head comparisons, clinicians and smokers lack a strong empirical basis for recommending or selecting from the available smoking cessation medications. Finally, the small number of studies offering head-to-head comparisons yield some conflicting evidence.^{6,7}

Five pharmacotherapies were selected for comparison in this placebo-controlled trial: nicotine lozenge, nicotine patch, bupropion, nicotine patch plus nicotine lozenge, and bupropion plus nicotine lozenge.¹ These therapies were selected for several reasons. The nicotine lozenge was selected because there was limited evidence regarding its efficacy. The 2008 PHS Guideline Update identified only 1 randomized placebo-controlled trial that evaluated the lozenge and thus gave the lozenge a B-level strength-of-evidence rating. The single placebo-controlled trial on the lozenge suggests that it is both acceptable to smokers and highly efficacious.⁸

The nicotine patch was included in this study because it is the most commonly used pharmacotherapy for smoking cessation.^{6,9,10} Given that so many smokers use the nicotine patch, it is important to determine the efficacy of other agents relative to the patch. Finally, it is important to examine the efficacy of the patch because recent data suggest that patch efficacy may have declined over the past 5 to 10 years.¹¹⁻¹³

Bupropion SR was selected because there is modest evidence that it may be more efficacious than the nicotine patch.^{11,14} Also, bupropion has never been directly compared with the nicotine lozenge. Finally, smokers could be encouraged to seek out this prescribed agent, and insurers and health care systems could be encouraged to make this treatment more widely available, if it could be demonstrated that bupropion is more efficacious than over-the-counter medication (eg, the nicotine patch or lozenge).

In addition to the 3 monotherapies, we tested 2 combination therapies. Research has generally supported the efficacy of NRT combinations. The 2008 PHS Guideline identified long-term (>14 weeks) nicotine patch use paired with either nicotine gum or nicotine nasal spray as efficacious relative to placebo and relative to the nicotine patch alone.¹ A recent Cochrane meta-analysis also found that the nicotine patch plus fast-acting NRT was more effective than monotherapy.² Combination NRT could be superior to monotherapy for several reasons. For instance, the use of 2 NRTs might produce more adequate nicotine replacement (ie, higher blood nicotine levels¹⁵) than a single NRT, though high-dose nicotine patches have not been shown to produce higher abstinence rates than standard-dose patches on a consistent basis.^{1,2} Another possibility is that each type of agent works through a different mechanism, so that having 2 types produces additive effects. The patch, for instance, produces a

steady supply of nicotine to prevent severe nicotine withdrawal, and ad libitum NRTs (gum and lozenges) provide a means for coping with situational challenges and transient urges to smoke.^{15,16}

The combination of bupropion and the nicotine lozenge was also examined because of promising initial results with the nicotine lozenge as a monotherapy.¹⁷ Also, the combination of the nicotine patch with bupropion was found to be highly efficacious in the 2008 PHS Guideline meta-analysis (odds ratio [OR], 2.5).¹ It is possible that an NRT that permits ad libitum dosing would produce even better outcomes.

The current research evaluated the 5 pharmacotherapy interventions on a range of outcome indices, including 6-month 7-day point-prevalence quit rate, a traditional standard for assessing efficacy of smoking cessation interventions.¹ This research also determined whether the medications were efficacious in helping a smoker achieve early success (ie, being able to quit for a week following the quit date) or any success at all (ie, being able to establish abstinence for at least 1 day during the first week of a quit attempt). In addition, outcomes assessed whether different medications increased the time to first lapse (the first cigarette smoked after quitting) or the time to relapse (smoking on 7 consecutive days following the quit day) or prevented a lapse from becoming a relapse. These different outcomes may help researchers understand the mechanisms of action of different medications and may be helpful in cessation counseling. For instance, if a medication reduces the transition of a lapse to a relapse,¹⁸ smokers could be urged to continue medication use despite lapsing.

In sum, this research attempted to gauge the relative efficacies of widely available smoking cessation medications. The results were intended to permit more informed decisions about the selection and use of smoking cessation pharmacotherapies as a means of enhancing treatment effectiveness.

METHODS

PARTICIPANTS

Participants were 1504 smokers (58% female, 83% white) who agreed to participate in a 3-year smoking cessation (year 1) and health outcomes (years 2 and 3) study conducted in Madison and Milwaukee, Wisconsin (principal investigator, T.B.B.). Adult smokers were recruited via television, radio, and newspaper advertisements; flyers; earned media, including press conferences; and television and radio news interviews from January 2005 to June 2007. Inclusion criteria included smoking more than 9 cigarettes per day on average for at least the past 6 months, having an alveolar carbon monoxide level greater than 9 ppm, and being motivated to quit smoking. Exclusion criteria included using any form of tobacco other than cigarettes, currently taking bupropion, or having a current psychosis or schizophrenia diagnosis. In addition, participants were excluded if they had medical contraindications for any of the study medications, including high alcohol consumption (6 drinks per day on 6 or 7 days of the week), a history of seizure, high blood pressure (>160/100 mm Hg), bipolar disorder, an eating disorder, a recent cardiac event, or allergies to any of the medi-

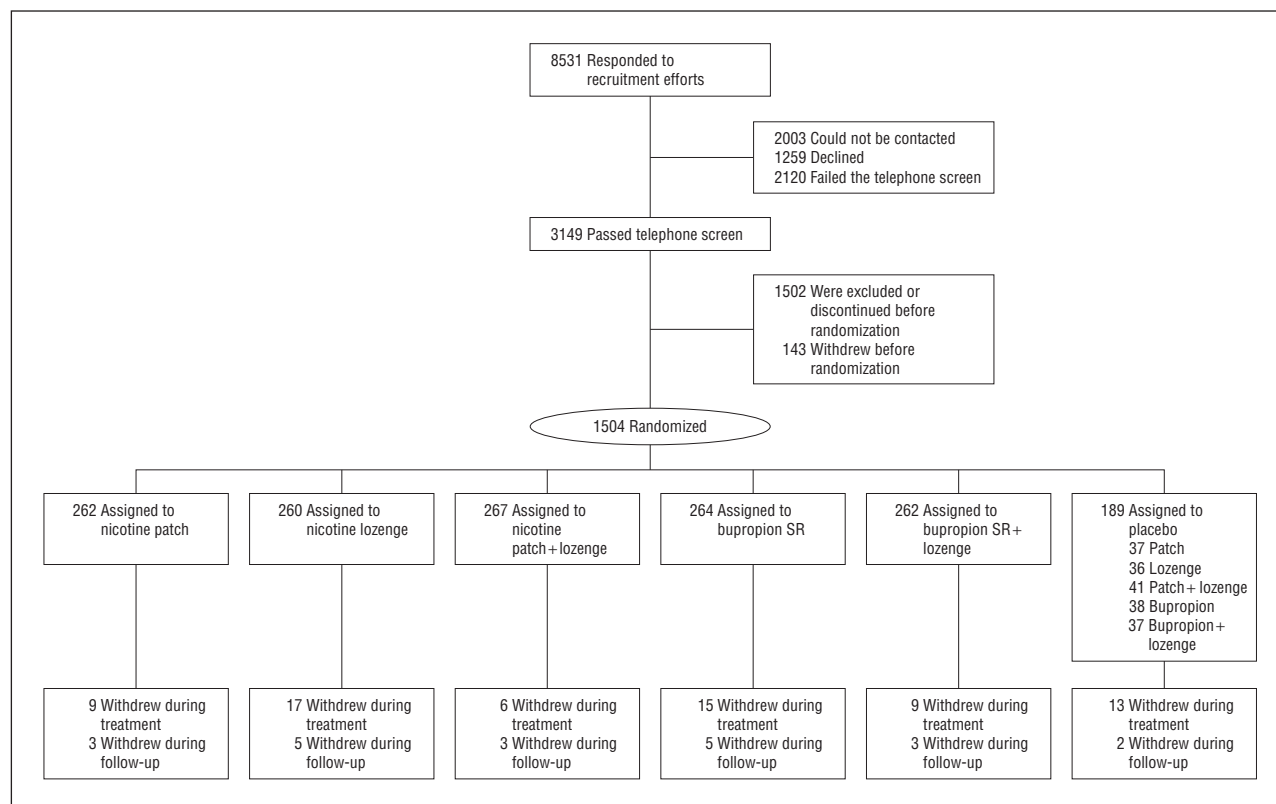


Figure 1. Flowchart of participants from study recruitment through screening, randomization, and follow-up. SR indicates sustained release.

cations. Only 1 person per household could participate. Finally, pregnant or breastfeeding women were not eligible for participation; eligible female participants had to agree to take steps to prevent pregnancy during the medication treatment phase of the study. All participants provided written informed consent and the study was approved by the University of Wisconsin Health Sciences institutional review board.

PROCEDURES

Interested smokers telephoned a central research office and completed a telephone screen to determine eligibility. Participants who passed the telephone screen were invited to an informational session where they provided written informed consent. Next, participants completed 3 in-person baseline sessions. During the first baseline session, participants underwent further screening, including collection of relevant medical history information, vital signs measurement, and a carbon monoxide breath test. Additionally, at this visit, participants completed several demographic, smoking history, and tobacco dependence questionnaires.

After additional medical assessments at 2 more baseline sessions (eg, brachial artery reactivity, carotid intima media thickness, and small-particle lipoprotein testing), participants were randomized to 1 of 6 treatment conditions: (1) bupropion SR (150 mg twice daily for 9 weeks total: 1 week prequit and 8 weeks postquit [prequit and postquit refer, respectively, to the periods prior to and following a patient's targeted quit date]); (2) nicotine lozenge (2 or 4 mg based on appropriate dose-for-dependence level per package instructions for 12 weeks postquit); (3) nicotine patch (24-hour patch; 21, 14, and 7 mg; titrated down during 8 weeks postquit); (4) nicotine patch (24-hour patch; 21, 14, and 7 mg; titrated down during 8 weeks postquit) plus nicotine lozenge (2 or 4 mg based on appropriate dose-for-

dependence level per package instructions for 12 weeks postquit) combination therapy; (5) bupropion SR (150 mg twice daily for 9 weeks total: 1 week prequit and 8 weeks postquit) plus nicotine lozenge (2 or 4 mg based on appropriate dose-for-dependence level per package instructions for 12 weeks postquit) combination therapy; or (6) placebo. There were 5 distinct placebo conditions, matched to each of the active treatment conditions (ie, placebo bupropion, placebo lozenge, placebo patch, placebo patch plus lozenge, and placebo bupropion plus lozenge) (**Figure 1**). Participants received study medication at each visit and returned any unused medication at the following visit. Randomization was double-blind and used a blocked randomization scheme with sex and self-reported race (white/nonwhite) as the blocking variables. Staff did not know to which type(s) of medication (ie, patch, pill, and/or lozenge) a participant would be assigned until the moment of randomization, and study staff were blinded to whether the medication was active or placebo. In addition to pharmacotherapy, all participants received 6 one-on-one counseling sessions based on the PHS Guideline.¹ Study staff who provided counseling and conducted study sessions were bachelor-level, trained case managers supervised by a licensed clinical psychologist. Sessions lasted 10 to 20 minutes and occurred during 7 weeks with the first 2 counseling sessions occurring prior to quitting and the subsequent 5 occurring on the quit date or thereafter (**Figure 2**). The last baseline visit, when randomization occurred and medication was dispensed, took place between 8 and 15 days prequit to ensure the bupropion up-titration schedule could be completed. Participants were instructed to start taking medications on the designated quit date, except for bupropion SR, which they were instructed to begin taking 1 week prior to the quit date as per the package insert instructions. Participants had study visits on their quit day and at 1, 2, 4, and 8 weeks postquit. At study visits, vital signs, adverse events, and smoking status were all recorded.

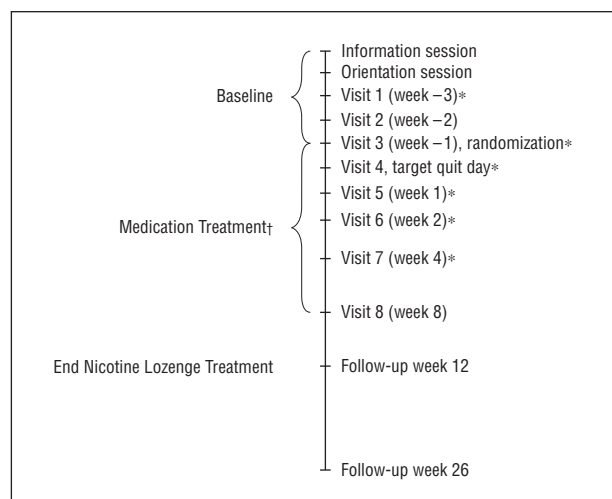


Figure 2. Study timeline including all study visits for both assessment as well as treatment. *Counseling session. †All treatments were administered through week 8 except for the lozenge, which was continued until week 12.

MAIN OUTCOME MEASURES

Demographics and Smoking

Baseline questionnaires assessed demographics, smoking history, and nicotine dependence. The demographics questionnaire measured characteristics such as sex, race (smokers were asked which race they most strongly identified with), Latino ethnicity (ie, reporting ≥ 1 parent of Latino origin), income, education level, and age. A smoking history questionnaire provided information about smoking behavior, smoking restrictions at home and work, self-efficacy to quit smoking, spouse smoking patterns, and motivation to quit smoking. Nicotine dependence questionnaires included the Fagerstrom Test of Nicotine Dependence,¹⁹ the Nicotine Dependence Syndrome Scale,²⁰ the Tobacco Dependence Screener,²¹ and the Wisconsin Inventory of Smoking Dependence Motives.²²

Smoking Status

Smoking status was assessed both as 7-day point-prevalence abstinence ("Have you smoked at all, even a puff, in the last 7 days?") and continuous abstinence (smoking at all since the target quit day), using a smoking calendar and the timeline follow-back method.^{23,24} All participants' self-reports of smoking status during study visits were confirmed by an expired carbon monoxide level of less than 10 ppm measured using a Micro-3 Smokerlyzer (Bedfont Scientific, Williamsburg, Virginia).

STATISTICAL ANALYSIS

All analyses were conducted using SPSS 15.0 software (SPSS Inc, Chicago, Illinois). After verifying that all treatment groups were similar across demographic and tobacco-related variables, we evaluated treatment effects on multiple outcome variables, including (1) carbon monoxide-confirmed 7-day point-prevalence abstinence at 1 week postquit, end of treatment (8 weeks postquit), and 6 months postquit; (2) number of days to lapse (latency to smoke a first cigarette after the target quit day); (3) number of days to relapse (latency to smoke on 7 consecutive days after the target quit day); (4) latency to relapse after the first lapse; and (5) initial cessation (whether the participant went ≥ 1 day without smoking in the first week postquit; due to missing data, $n=1424$ for this outcome). Logistic re-

gression was used for dichotomous outcomes (eg, 7-day point-prevalence abstinence), while Cox regression was used for continuous outcomes (eg, latency to lapse).

We conducted 11 comparisons for each outcome, which constituted a family of analyses that compared each active treatment with placebo (5 comparisons), each monotherapy with the other (3 comparisons), the 2 combination therapies with each other (2 comparisons), and a composite of the monotherapies with the bupropion plus lozenge combination and the patch plus lozenge combination (2 comparisons). To control for the familywise error when conducting multiple tests, we used a Bonferroni-corrected P value ($P=.0045$) for the 11 comparisons for an overall $\alpha=.05$ (all tests 2-sided). We report both adjusted as well as unadjusted P values. All analyses were conducted using the intent-to-treat principle such that all smokers who were randomized to a treatment were included in the analyses and individuals with missing data were considered to be smoking. Analyses were also conducted controlling for race (white vs nonwhite), sex, and site. This study had an a priori power of 0.88 to detect a clinically significant improvement in abstinence rates of 12% at 6 months posttreatment (eg, 12% vs 24%), with no correction for multiple comparisons ($\alpha=.05$) and a power of 0.60 for the Bonferroni-corrected $\alpha=.005$. To detect an improvement in abstinence rates of 15% (eg, 12% vs 27%), this study had an a priori power of 0.97 for $\alpha=.05$ and a power of 0.84 for $\alpha=.005$.

RESULTS

Table 1 provides demographics and smoking history data for the 1504 adult smokers who were randomized in this double-blind placebo-controlled smoking cessation study. There were no statistically significant differences between the active and placebo treatment groups by age, cigarettes smoked per day, Fagerstrom Test of Nicotine Dependence score, baseline carbon dioxide level, sex, marital status, race, Latino origin, or education. Figure 1 presents the study's CONSORT data.

There were no statistically significant differences among the placebo conditions in 7-day point-prevalence outcomes at 1 week, end of treatment, or 6 months postquit. Therefore, for all subsequent analyses, the placebo conditions were combined into a unified placebo condition.

There was a significant main effect for study site, such that, relative to Madison, Milwaukee had significantly lower 7-day point-prevalence abstinence rates at all 3 follow-up points. However, there were no treatment by site interactions, and analyses that controlled for site produced results similar to those in the uncontrolled analyses.

EFFICACY

Comparing all 5 active treatments with the placebo group in 7-day point-prevalence analyses and using an uncorrected $P=.05$, logistic regression analysis indicated that all active treatments produced higher rates of initial cessation and higher 7-day point-prevalence abstinence rates at 1 week, end of treatment, and 6 months postquit (with the exception of the lozenge at 1 week) relative to placebo (**Table 2** and **Table 3**). The ORs at 6 months postquit were 1.63 for bupropion, 1.76 for lozenges, 1.83 for the patch, 1.74 for bupropion plus lozenge, and 2.34 for patch plus lozenge. With corrected $P=.0045$, only the patch and the 2 combination therapies were efficacious

Table 1. Demographic and Smoking History for the Total Sample and by Treatment Group

| Characteristic | No. (%) | | | | | | |
|--|---------------------|----------------------|------------------------|----------------------|--------------------|-------------------------------------|---------------------------------|
| | Total (N = 1504) | Placebo (n = 189) | Bupropion (n = 264) | Lozenge (n = 260) | Patch (n = 262) | Bupropion + Lozenge (n = 262) | Patch + Lozenge (n = 267) |
| Female sex | 876 (58.2) | 111 (58.7) | 154 (58.3) | 151 (58.1) | 153 (58.4) | 154 (58.8) | 153 (57.3) |
| Married | 667 (44.5) | 77 (40.7) | 117 (44.5) | 116 (44.6) | 114 (43.8) | 128 (49.2) | 115 (43.1) |
| Employed for wages | 1020 (67.8) | 124 (65.6) | 182 (68.9) | 181 (69.6) | 177 (67.6) | 184 (70.2) | 172 (64.4) |
| High school education only | 353 (23.6) | 48 (25.8) | 52 (19.7) | 61 (23.5) | 73 (28.2) | 61 (23.5) | 58 (21.8) |
| Race/ethnicity ^a | | | | | | | |
| Latino ^b | 42 (2.8) | 7 (3.7) | 7 (2.7) | 5 (1.9) | 6 (2.3) | 8 (3.1) | 9 (3.4) |
| White | 1258 (83.9) | 160 (84.7) | 221 (83.7) | 217 (83.5) | 220 (84.6) | 217 (83.5) | 223 (83.5) |
| African American | 204 (13.6) | 20 (10.6) | 35 (13.3) | 38 (14.6) | 35 (13.5) | 38 (14.6) | 38 (14.2) |
| Other | 38 (2.6) | 9 (4.7) | 8 (3.0) | 5 (1.9) | 5 (1.9) | 5 (1.9) | 6 (1.9) |
| Age, mean (SD), y | 44.7 (11.1) | 43.1 (11.4) | 43.9 (11.7) | 45.3 (10.4) | 44.9 (11.6) | 45.3 (10.4) | 44.2 (11.1) |
| Previous quit attempts, mean (SD) | 5.7 (9.7) | 6.2 (13.1) | 6.2 (10.4) | 5.7 (11.2) | 5.9 (10.1) | 5.0 (5.2) | 5.3 (6.5) |
| FTND total score | 5.4 (2.1) | 5.5 (2.2) | 5.4 (2.2) | 5.2 (2.2) | 5.4 (2.1) | 5.3 (2.1) | 5.5 (2.1) |
| Cigarettes smoked/d, mean (SD) | 21.4 (8.9) | 21.0 (8.3) | 21.4 (8.2) | 21.6 (9.1) | 21.4 (9.2) | 21.0 (8.5) | 21.93 (9.6) |
| Baseline carbon monoxide level, mean (SD) | 25.8 (12.5) | 24.5 (13.3) | 25.0 (10.7) | 24.6 (12.0) | 26.4 (12.3) | 26.8 (13.6) | 26.8 (12.2) |

Abbreviation: FTND, Fagerstrom Test of Nicotine Dependence.

^aSmokers were asked with which race they most strongly identified.

^bSmokers who reported that at least 1 parent was of Latino origin.

Table 2. Carbon Dioxide–Confirmed Point-Prevalent Abstinence and Initial Cessation Rates^a

| Smoking Cessation/Abstinence | Rate, % | | | | | |
|--------------------------------|---------|-----------|---------|-------|------------------------|--------------------|
| | Placebo | Bupropion | Lozenge | Patch | Bupropion + Lozenge | Patch + Lozenge |
| Initial cessation ^b | 69.4 | 82.2 | 81.3 | 87.7 | 84.5 | 91.5 |
| Abstinence | | | | | | |
| 1 wk | 23.3 | 34.5 | 29.2 | 40.5 | 37.4 | 43.4 |
| 8 wk, end of treatment | 30.2 | 40.2 | 40.4 | 44.7 | 50.4 | 53.6 |
| 6 mo | 22.2 | 31.8 | 33.5 | 34.4 | 33.2 | 40.1 |

^aDue to missing data, n = 1424 for this analysis.

^bInitial cessation is defined as at least 1 day of abstinence during the first 7 days after the target quit day.

at 1 week and the end of treatment, and only the patch plus lozenge condition was efficacious at 6 months postquit (Table 2 and Table 3). Using the corrected *P* values, all treatments, except the lozenge, significantly increased the rates of initial cessation (not smoking for at least 1 day in the first week postquit). The same effects were obtained when logistic regression analyses controlled for race, sex, and site.

Survival analyses (Cox regression) revealed that relative to placebo all active treatments significantly increased the number of days to relapse using both the unadjusted ($P < .05$) as well as the Bonferroni-corrected *P* value ($P \leq .001$). Only the 2 combination conditions significantly increased the number of days to lapse relative to placebo when using the Bonferroni-corrected *P* value ($P < .001$). **Figure 3** illustrates the survival curves for latency to relapse. The survival curves for latency to lapse and for latency to relapse following a lapse were similar to the survival curves for latency to relapse. All active treatments increased the latency to relapse following the first lapse ($P \leq .003$) with the exception of the lozenge (Wald=6.39, $P = .01$, OR, 0.73; 95% confidence interval

[CI], 0.75-0.93). The same effects were obtained when analyses controlled for race, sex, and site.

The bupropion plus lozenge condition and the patch plus lozenge condition were both compared with a composite monotherapy condition to determine whether either of the combination conditions was superior to monotherapy. Results of logistic regression analyses revealed that, relative to the monotherapies, the patch plus lozenge treatment produced significantly higher initial cessation rates and end of treatment abstinence rates (Table 3), using the Bonferroni-corrected *P* value. There were no other differences between the combination conditions and the composite monotherapy condition. The results were similar after controlling for race, sex, and site. It should be noted that there were no significant differences either between the 2 combination conditions or among the monotherapy conditions at any of the time points using the Bonferroni-corrected *P* value.

With respect to the latency outcome variables, Cox regression analyses revealed that patch plus lozenge users had a greater latency to lapse, relative to the composite monotherapy condition (Wald=7.31; $P = .007$; OR,

Table 3. Logistic Regressions Predicting Initial Cessation and Point-Prevalent Abstinence

| Treatment | Initial Cessation | | | 1 wk Postquit | | |
|---|-------------------|--------------------|------------------|---------------|--------------------|------------------|
| | Wald | P Value | OR (95% CI) | Wald | P Value | OR (95% CI) |
| Relative to placebo | | | | | | |
| Bupropion | 9.25 | .002 ^a | 2.04 (1.29-3.22) | 6.52 | .01 | 1.73 (1.14-2.64) |
| Lozenge | 7.60 | .006 | 1.91 (1.21-3.03) | 1.97 | .16 | 1.36 (.89-2.09) |
| Patch | 20.32 | <.001 ^a | 3.14 (1.91-5.17) | 14.29 | <.001 ^a | 2.24 (1.47-3.40) |
| Bupropion + lozenge | 13.14 | <.001 ^a | 2.40 (1.50-3.84) | 10.00 | .002 ^a | 1.97 (1.29-3.00) |
| Patch + lozenge | 31.18 | <.001 ^a | 4.73 (2.74-8.16) | 19.23 | <.001 ^a | 2.53 (1.67-3.83) |
| Relative to monotherapies | | | | | | |
| Bupropion + lozenge | 0.07 | .79 | 1.05 (0.71-1.56) | 0.61 | .43 | 1.12 (0.84-1.50) |
| Patch + lozenge | 9.01 | .003 ^a | 2.08 (1.29-3.36) | 6.46 | .01 | 1.44 (1.09-1.92) |
| Monotherapies relative to each other ^b | | | | | | |
| Patch vs lozenge | 3.86 | .049 | 0.61 (0.37-0.99) | 7.20 | .007 | 0.61 (0.42-0.88) |
| Bupropion vs lozenge | 0.07 | .78 | 0.94 (0.59-1.48) | 1.65 | .20 | 0.79 (0.54-1.14) |
| Patch vs bupropion | 2.94 | .09 | 0.65 (0.40-1.06) | 2.01 | .16 | 0.77 (0.54-1.10) |
| Patch + lozenge vs bupropion + lozenge | 5.77 | .02 | 0.51 (0.29-0.88) | 2.00 | .16 | 0.78 (0.55-1.10) |

| Treatment | End of Treatment, 8 wk Postquit | | | 6 mo Postquit | | |
|---|---------------------------------|--------------------|------------------|---------------|--------------------|------------------|
| | Wald | P Value | OR (95% CI) | Wald | P Value | OR (95% CI) |
| Relative to placebo | | | | | | |
| Bupropion | 4.75 | .03 | 1.55 (1.05-2.31) | 5.01 | .03 | 1.63 (1.06-2.51) |
| Lozenge | 4.93 | .03 | 1.57 (1.05-2.33) | 6.68 | .01 | 1.76 (1.15-2.70) |
| Patch | 9.64 | .002 ^a | 1.87 (1.26-2.77) | 7.70 | .006 | 1.83 (1.20-2.81) |
| Bupropion + lozenge | 18.10 | <.001 ^a | 2.35 (1.59-3.49) | 6.42 | .01 | 1.74 (1.13-2.67) |
| Patch + lozenge | 24.02 | <.001 ^a | 2.67 (1.80-3.96) | 15.65 | <.001 ^a | 2.34 (1.54-3.57) |
| Relative to monotherapies | | | | | | |
| Bupropion + lozenge | 5.95 | .02 | 1.42 (1.07-1.88) | 0.00 | >.99 | 1.00 (0.74-1.35) |
| Patch + lozenge | 11.19 | .001 ^a | 1.61 (1.22-2.13) | 4.12 | .04 | 1.35 (1.01-1.79) |
| Monotherapies relative to each other ^b | | | | | | |
| Patch vs lozenge | 0.97 | .32 | 0.84 (0.59-1.19) | 0.05 | .83 | 0.96 (0.67-1.38) |
| Bupropion vs lozenge | 0.003 | .96 | 1.01 (0.71-1.43) | 0.38 | .54 | .89 (0.62-1.28) |
| Patch vs bupropion | 1.09 | .30 | 0.83 (0.59-1.18) | 0.38 | .54 | .89 (0.62-1.28) |
| Patch + lozenge vs bupropion + lozenge | 0.53 | .47 | 0.88 (0.63-1.24) | 2.68 | .10 | 0.74 (0.52-1.06) |

Abbreviations: CI, confidence interval; OR, odds ratio.

^a $P < .005$, Bonferroni-corrected for 11 comparisons with $\alpha = .05$.

^b First condition listed is the reference condition.

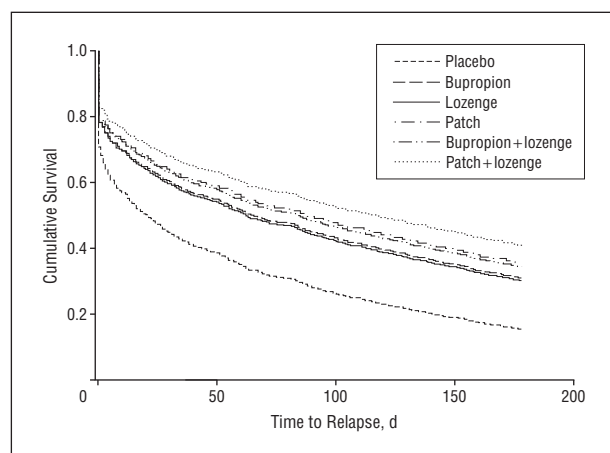


Figure 3. Survival curves for latency to relapse, or the number of days until the participants smoked on 7 consecutive days following the target quit day for the 6 treatment conditions.

0.80; 95% CI, 0.78-0.94); a similar effect was found for number of days to relapse (Wald = 5.45; $P = .02$; OR, 0.79; 95% CI, 0.64-0.96). These differences were not significant with the Bonferroni correction ($P < .005$). Even with-

out the Bonferroni correction, there were no differences among the combination and monotherapy groups in latency to relapse after smoking the first cigarette (ie, after lapsing). The same effects were obtained when analyses controlled for race, sex, and site.

MEDICATION USE

At each visit, participants were given additional medication and asked to return any that was unused. We computed the percentage of medication each participant used by subtracting the amount of medication the participant returned from the amount of medication given to the participant and then dividing that by the total amount of medication given to the participant. On average, participants used approximately 77% of the medication given during the course of the study (placebo, 75%; patch, 86%; bupropion, 85%; lozenge, 67%; bupropion plus lozenge, 77%; and patch plus lozenge, 74%). A 1-way analysis of variance revealed significant differences in the amount of medication used by treatment condition ($F_{5,1187} = 17.64$, $P < .001$). Post hoc Tukey tests revealed that individuals in the lozenge condition used significantly less medication (67% of the medi-

Table 4. Adverse Events by Treatment Condition

| Adverse Event | No. (%) | | | | | |
|---------------------------------------|----------------------|------------------------|----------------------|--------------------|----------------------------------|------------------------------|
| | Placebo (n = 189) | Bupropion (n = 262) | Lozenge (n = 260) | Patch (n = 264) | Bupropion + Lozenge (n = 267) | Patch + Lozenge (n = 262) |
| Nausea | 16 (4.4) | 20 (3.8) | 44 (7.8) | 25 (4.3) | 33 (5.0) | 55 (7.9) |
| Skin irritation | 10 (2.7) | 14 (2.7) | 3 (1.0) | 86 (14.7) | 14 (2.1) | 62 (8.9) |
| Dizziness | 6 (1.7) | 6 (1.1) | 5 (1.0) | 7 (1.2) | 15 (2.3) | 9 (1.3) |
| Diarrhea | 4 (1.1) | 8 (1.5) | 13 (2.3) | 8 (1.4) | 11 (1.7) | 6 (1.0) |
| Vomiting | 4 (1.1) | 10 (1.9) | 8 (1.4) | 4 (1.0) | 9 (1.4) | 11 (1.6) |
| Dry mouth | 3 (1.0) | 20 (3.8) | 0 (0.0) | 1 (0.2) | 25 (3.8) | 2 (0.2) |
| Mouth/throat irritation | 12 (3.3) | 11 (2.1) | 38 (6.7) | 11 (1.9) | 15 (2.3) | 40 (5.7) |
| Alteration of taste | 2 (1.0) | 8 (1.5) | 1 (0.2) | 0 | 9 (1.4) | 0 |
| Sleep disturbance and abnormal dreams | 20 (5.6) | 88 (16.8) | 18 (3.2) | 66 (11.3) | 69 (10.6) | 63 (9.0) |
| Flatulence/gas | 5 (1.4) | 1 (0.2) | 16 (2.8) | 0 | 28 (4.3) | 15 (2.1) |
| Hiccups | 1 (0.3) | 0 | 35 (6.2) | 0 | 7 (1.1) | 22 (3.2) |
| Headaches | 24 (6.7) | 23 (4.4) | 29 (5.1) | 26 (4.4) | 30 (4.6) | 34 (4.9) |
| Dyspepsia, heartburn and indigestion | 4 (1.1) | 3 (1.0) | 1 (0.2) | 4 (1.0) | 23 (3.5) | 25 (3.6) |
| Total | 359 | 524 | 566 | 585 | 654 | 697 |

cation given) than individuals in any of the other treatment conditions ($P = .03$ to $<.001$).

SAFETY

The most common adverse events varied by treatment group but were consistent with previous research. In the placebo condition, the most common adverse events were headaches, skin irritation in the patch condition, sleep disturbances/abnormal dreams in the bupropion condition, nausea in the lozenge condition, sleep disturbances/abnormal dreams in the bupropion plus lozenge condition, and both sleep disturbances/abnormal dreams and skin irritation in the patch plus lozenge condition (**Table 4**). Participants in the combination conditions (patch plus lozenge and bupropion plus lozenge) reported more adverse events than those in either the monotherapy or placebo groups. There were 32 serious adverse events during the 6-month period following the target quit day (eg, hospitalization for pneumonia or due to falling), but only 1 serious adverse event, hospitalization for seizures, was possibly related to study medication. Seizures are an identified potential adverse effect of bupropion, which the participant was taking at the time of the seizure. Four people (0.27%) withdrew from the study owing to events related to medication: 1 in the bupropion group because it interacted with other antidepressants and the participant's physician requested that the participant withdraw, 1 in the bupropion group because of heartburn, 1 because of a "negative experience" while taking placebo medication, and 1 in the bupropion plus lozenge condition owing to hospitalization for seizures.

COMMENT

A principal goal of this research was to identify particularly efficacious smoking cessation pharmacotherapy interventions among the 5 different treatments tested in a head-to-head comparison. The nicotine patch plus loz-

enge combination emerged as the treatment with the strongest support. Its OR at 6 months postquit was 2.34, while the next highest OR was 1.83 (for the nicotine patch). The nicotine patch plus lozenge combination emerged as the only efficacious treatment (after Bonferroni correction for multiple tests) relative to placebo at 6 months postquit. In addition, relative to a monotherapy composite, the patch plus lozenge condition produced higher initial cessation rates and end-of-treatment 7-day point-prevalence rates using the Bonferroni-corrected α level. The patch plus lozenge combination also tended to produce more positive outcomes than any other condition, active or placebo, on measures such as days to lapse and days to relapse (Figure 3); these differences did not exceed protection levels for multiple comparisons, however. These effects are consistent with previous research showing that the patch plus ad libitum NRT increases the time to relapse.²⁵ Finally, while there was substantial evidence that the patch plus lozenge combination was highly efficacious relative to the placebo condition, it is important to note that its 6-month outcome did not differ significantly from the other active cessation treatments in head-to-head comparisons.

While the patch plus lozenge combination was notably efficacious relative to placebo, the other pharmacotherapies were also significantly effective if tested using unadjusted P values (Table 3). These pharmacotherapies, with ORs ranging from 1.63 to 1.83, would have been found to be efficacious relative to placebo had they been tested in a typical randomized clinical trial involving only a single active treatment and a placebo control. Thus, the current results suggest that there was a relatively strong effect of the patch plus lozenge vs placebo, rather than unusually weak effects of the other interventions. This pattern of findings should be evaluated in light of the relatively high abstinence rates that occurred in the placebo condition. At 6 months postquit, participants in the placebo group achieved a 22.2% abstinence rate. This abstinence rate is larger than many 6-month

abstinence rates in active treatment conditions in other studies.^{7,11} The success of placebo may have been due to the intensive counseling participants received (6 sessions, totaling more than 60 minutes of counseling)²⁶ or to the high level of motivation required to participate in a 3-year longitudinal trial.

During treatment, the patch, bupropion plus lozenge, and patch plus lozenge conditions were all significantly more efficacious than placebo with the familywise error correction. However, after treatment was discontinued, by 6 months postquit only the patch plus lozenge remained efficacious. These findings agree with the 2008 Guideline Update meta-analyses that showed that the combination of long-term patch plus gum or spray had the highest OR for efficacy (6-month abstinence) of any of the evaluated pharmacotherapies (monotherapies and combination therapies) when tested against a placebo control condition (OR, 3.6).¹ These findings suggest that long-term pharmacotherapy (>14 weeks), particularly with the nicotine patch, may be important given that the effects of bupropion plus lozenge diminished significantly once participants stopped using them at the end of treatment. Future research should examine relapse dynamics following the discontinuation of treatment; it would be important to know if treatment discontinuation was more consequential for some pharmacotherapies than for others.^{27,28} Future research should also address the promising issue of using pharmacotherapy prior to the quit attempt.^{1,2}

One of the outcomes assessed in this research was whether pharmacotherapy treatment could help people achieve at least 1 day of abstinence (initial cessation). The ability to achieve initial abstinence is not only a stepping stone to successful quitting, but research suggests that duration of abstinence in prior quit attempts enhances success in subsequent attempts.²⁹⁻³¹ In this regard, the patch and patch plus lozenge conditions resulted in the highest rates of initial abstinence (using adjusted *P* values) (Table 2). This finding is consistent with earlier findings that the high-dose nicotine patch was significantly more effective in helping smokers achieve initial abstinence relative to placebo.¹⁸ It should be noted that bupropion alone and bupropion plus lozenge also had significantly higher initial cessation rates relative to placebo using adjusted *P* values.

Previous research on combination NRT paired the patch with nicotine gum,^{25,32} nicotine nasal spray,^{7,33} or a nicotine inhaler.^{34,35} The present results suggest that the nicotine lozenge can also be effective as an adjuvant to the nicotine patch. The key seems to be that an ad libitum, or as needed, agent must be paired with the patch; simply using higher patch doses does not seem to augment outcomes to the same degree.³⁶⁻³⁹ While the nicotine lozenge appears to be an effective patch adjuvant, its performance as a monotherapy was not as impressive as the patch. For instance, the lozenge did not produce significantly higher cessation rates than placebo in either the first week of treatment or at the end of treatment (with α adjustment) (Table 3).

While overall medication adherence reached an average of 77%, there were significant differences in rates of use of the different medications. Bupropion and the nicotine patch had the highest use rates followed by the

2 combinations; the nicotine lozenge had the lowest use rates. These findings suggest that smokers are especially unlikely to use as needed medications adherently (ie, a recommendation of 9 lozenges per day). This is consistent with other literature that suggests an inverse relation between the number of doses prescribed and medication adherence⁴⁰ and with research showing a direct positive relation between medication adherence and cessation outcome.⁴¹⁻⁴⁶

The pharmacotherapy interventions used in this research appear to be safe and well tolerated. Only 4 individuals out of 1504 withdrew from the study for medication-related reasons. There were more adverse events, however, among individuals in the combination pharmacotherapy vs the monotherapy or placebo conditions (Table 4). Combination therapy did not appear to increase serious adverse events or study withdrawal compared with monotherapy. These findings agree with prior research that supported the safety and patient acceptance of combination NRT.^{15,25,32,47,48}

One limitation of this study is that treatment took place in the context of a longitudinal study, which may have selected participants with greater motivation to quit than smokers in the general population. In addition, treatment lasted only 8 weeks (with the exception of the nicotine lozenge, which lasted for 12 weeks). Future research will be needed to determine whether long-term use of these pharmacotherapies improves efficacy (though some evidence suggests that longer use is not efficacious¹). A final limitation is that the study did not include varenicline among the tested medications (varenicline was not approved by the Food and Drug Administration at the time of study initiation), and therefore it is unknown how these agents would have fared relative to varenicline, the monotherapy designated as most effective by the 2008 PHS Guideline.¹ The results do suggest the importance of testing varenicline against a combination of the nicotine patch and an ad libitum NRT medication, as we identified this intervention to be especially efficacious relative to placebo.

In this study assessing 5 different pharmacotherapy interventions, the nicotine patch plus lozenge produced the greatest benefit relative to placebo. These findings plus recent meta-analyses published in the 2008 PHS Guideline Update suggest that a combination pharmacotherapy comprising the nicotine patch and an ad libitum NRT should be routinely considered for use as a smoking cessation treatment. In addition, this study illustrates that after more than 20 years the patch remains a highly efficacious pharmacotherapy for helping people quit smoking.

Submitted for Publication: October 31, 2008; final revision received April 1, 2009; accepted April 3, 2009.

Correspondence: Megan E. Piper, PhD, Center for Tobacco Research and Intervention, 1930 Monroe St, Ste 200, Madison, WI 53711 (p@ctri.medicine.wisc.edu).

Financial Disclosure: The authors report the following potential conflicts of interest for the last 5 years: Dr Smith has received research support from Elan Corporation. Dr Baker has served as an investigator on research projects

sponsored by pharmaceutical companies, including Sanofi-Synthelabo, Pfizer Inc, and Nabi Biopharmaceuticals. Dr Jorenby has received research support from the National Institute on Drug Abuse, the National Cancer Institute, Pfizer Inc, Sanofi-Synthelabo, and Nabi Biopharmaceuticals. He has received support for educational activities from the National Institute on Drug Abuse and the Veterans Administration and consulting fees from Nabi Biopharmaceuticals. Dr Fiore has received honoraria from Pfizer. He has served as an investigator on research studies at the University of Wisconsin that were funded by Pfizer, Sanofi-Synthelabo, GlaxoSmithKlein, and Nabi Biopharmaceuticals. In 1998, the University of Wisconsin appointed Dr Fiore to a named chair funded by an unrestricted gift to University of Wisconsin from Glaxo Wellcome. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding/Support: This research was conducted at the University of Wisconsin–Madison and was supported by grant P50 DA019706 from the National Institute on Drug Abuse and by grant M01 RR03186 from the General Clinical Research Centers Program of the National Center for Research Resources. Dr Piper was supported by an Institutional Clinical and Translational Science Award, University of Wisconsin–Madison (KL2 grant 1KL2RR025012-01). Medication was provided to patients at no cost under a research agreement with GlaxoSmithKline.

Disclaimer: No part of the manuscript was written or edited by anyone employed by a pharmaceutical company. The authors are solely responsible for the analyses, content, and writing of this article.

REFERENCES

1. Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: US Department of Health and Human Services, US Public Health Service; 2008.
2. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2008;(1):CD000146.
3. Hughes JR, Stead L, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2007;(1):CD000031.
4. Cahill K, Stead L, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2007;(1):CD006103.
5. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med*. 1997;337(8):536-542.
6. West R, Hajek P, Nilsson F, Foulds J, May S, Meadows A. Individual differences in preferences for and responses to four nicotine replacement products. *Psychopharmacology (Berl)*. 2001;153(2):225-230.
7. Croghan GA, Sloan JA, Croghan IT, Novotny P, Hurt RD, DeKrey WL, Mailliard JA, Ebbert LP, Swan DK, Walsh DJ, Wiesenfeld M, Levitt R, Stella P, Johnson PA, Tschetter LK, Loprinzi C. Comparison of nicotine patch alone versus nicotine nasal spray alone versus a combination for treating smokers: a minimal intervention, randomized multicenter trial in a nonspecialized setting. *Nicotine Tob Res*. 2003;5(2):181-187.
8. Shiffman S, Dresler CM, Hajek P, Gilbert SJA, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med*. 2002;162(11):1267-1276.
9. Burton SL, Gitchell JG, Shiffman S; Centers for Disease Control and Prevention. Use of FDA-approved pharmacological treatments for tobacco dependence: United States, 1984-1998. *MMWR Morb Mortal Wkly Rep*. 2000;49(29):665-668.
10. Pierce JP, Gilpin E, Farkas AJ. Nicotine patch use in the general population: results from the 1993 California Tobacco Survey. *J Natl Cancer Inst*. 1995;87(2):87-93.

11. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med*. 1999;340(9):685-691.
12. Pierce JP, Gilpin EA. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *JAMA*. 2002;288(10):1260-1264.
13. Irvin JE, Hendricks PS, Brandon TH. The increasing recalcitrance of smokers in clinical trials II: pharmacotherapy trials. *Nicotine Tob Res*. 2003;5(1):27-35.
14. Gold PB, Rubey RN, Harvey RT. Naturalistic, self-assignment comparative trial of bupropion SR, a nicotine patch, or both for smoking cessation treatment in primary care. *Am J Addict*. 2002;11(4):315-331.
15. Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. *CNS Drugs*. 2001;15(6):453-467.
16. Shiffman S, Shadel WG, Niaura R, Khayrallah MA, Jorenby DE, Ryan CF, Ferguson CL. Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. *Psychopharmacology (Berl)*. 2003;166(4):343-350.
17. Shiffman S, Dresler CM, Rohay JM. Successful treatment with a nicotine lozenge of smokers with prior failure in pharmacological therapy. *Addiction*. 2004;99(1):83-92.
18. Shiffman S, Scharf DM, Shadel WG, Gwaltney CJ, Dang Q, Paton SM, Clark DB. Analyzing milestones in smoking cessation: illustration in a nicotine patch trial in adult smokers. *J Consult Clin Psychol*. 2006;74(2):276-285.
19. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. 1991;86(9):1119-1127.
20. Shiffman S, Waters A, Hickcox M. The Nicotine Dependence Syndrome scale: a multidimensional measure of nicotine dependence. *Nicotine Tob Res*. 2004;6(2):327-348.
21. Kawakami N, Takatsuka N, Inaba S, Shimizu H. Development of a screening questionnaire for tobacco/nicotine dependence according to ICD-10, DSM-III-R, and DSM-IV. *Addict Behav*. 1999;24(2):155-166.
22. Piper ME, Piasecki TM, Federman EB, Bolt DM, Smith SS, Fiore MC, Baker TB. A multiple motives approach to tobacco dependence: The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). *J Consult Clin Psychol*. 2004;72(2):139-154.
23. Sobell LC, Sobell MB, Leo GI, Cancilla A. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict*. 1988;83(4):393-402.
24. Brigham J, Lessov-Schlaggar CN, Javitz HS, McElroy M, Krasnow R, Swan GE. Reliability of adult retrospective recall of lifetime tobacco use. *Nicotine Tob Res*. 2008;10(2):287-299.
25. Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med*. 1995;24(1):41-47.
26. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ*. 2000;321(7257):355-358.
27. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR; Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):64-71.
28. Hurt RD, Krook JE, Croghan IT, Loprinzi CL, Sloan JA, Novotny PJ, Kardinal CG, Knost JA, Tirona MT, Addo F, Morton RF, Michalak JC, Schaefer PL, Porter PA, Stella PJ. Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. *J Clin Oncol*. 2003;21(5):914-920.
29. Alessi SM, Badger GJ, Higgins ST. An experimental examination of the initial weeks of abstinence in cigarette smokers. *Exp Clin Psychopharmacol*. 2004;12(4):276-287.
30. Nides MA, Rakos RF, Gonzales D, Murray RP, Tashkin DP, Bjornson-Benson WM, Lindgren P, Connett JE. Predictors of initial smoking cessation and relapse through the first 2 years of the Lung Health Study. *J Consult Clin Psychol*. 1995;63(1):60-69.
31. Swan GE, Jack LM, Javitz HS, McAfee T, McClure JB. Predictors of 12-month outcome in smokers who received bupropion sustained-release for smoking cessation. *CNS Drugs*. 2008;22(3):239-256.
32. Puska P, Korhonen HJ, Vartiainen E, Urjanheimo EL, Gustavsson G, Westin A. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. *Tob Control*. 1995;4(3):231-235.
33. Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ*. 1999;318(7179):285-288.
34. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med*. 2000;160(20):3128-3134.

35. Tønnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. *Eur Respir J*. 2000;16(4):717-722.
36. Dale LC, Hurt RD, Offord KP, Lawson GM, Croghan IT, Schroeder DR. High-dose nicotine patch therapy: percentage of replacement and smoking cessation. *JAMA*. 1995;274(17):1353-1358.
37. Kalman D, Kahler CW, Tirsch D, Kaschub C, Penk W, Monti PM. Twelve-week outcomes from an investigation of high-dose nicotine patch therapy for heavy smokers with a past history of alcohol dependence. *Psychol Addict Behav*. 2004;18(1):78-82.
38. Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy? *Exp Clin Psychopharmacol*. 1999;7(3):226-233.
39. Jorenby DE, Smith SS, Fiore MC, Hurt RD, Offord KP, Croghan IT, Hays JT, Lewis SF, Baker TB. Varying nicotine patch dose and type of smoking cessation counseling. *JAMA*. 1995;274(17):1347-1352.
40. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-1310.
41. Lam TH, Abdullah AS, Chan SS, Hedley AJ; Hong Kong Council on Smoking and Health Smoking Cessation Health Centre (SCHC) Steering Group. Adherence to nicotine replacement therapy versus quitting smoking among Chinese smokers: a preliminary investigation. *Psychopharmacology (Berl)*. 2005;177(4):400-408.
42. Mooney ME, Reus VI, Gorecki J, Hall SM, Humfleet GL, Muñoz RF, Delucchi K. Therapeutic drug monitoring of nortriptyline in smoking cessation: a multistudy analysis. *Clin Pharmacol Ther*. 2008;83(3):436-442.
43. Alterman AI, Gariti P, Cook TG, Cnaan A. Nicodermal patch adherence and its correlates. *Drug Alcohol Depend*. 1999;53(2):159-165.
44. Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, Wiseman D. Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction*. 1995;90(1):31-42.
45. Killen JD, Fortmann SP, Davis L, Varady A. Nicotine patch and self-help video for cigarette smoking cessation. *J Consult Clin Psychol*. 1997;65(4):663-672.
46. Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation. Who will quit with and without the nicotine patch. *JAMA*. 1994;271(8):589-594.
47. Haustein KO, Krause J, Haustein H, Rasmussen GI, Cort N. Comparison of the effects of combined nicotine replacement therapy vs. cigarette smoking in males. *Nicotine Tob Res*. 2003;5(2):195-203.
48. Fagerström KO, Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: a review. *Nicotine Tob Res*. 2002;4(suppl 2):S73-S79.